Metabolic Response to Acceleration in Man

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The glucose analogue 2-deoxy-D-glucose (2-DG) was used as a means of producing intracellular hypoglycemia in eight normal male volunteer subjects during a control period, immediately following their initial exposure to acceleration (acute acceleration) and following a fourth acceleration exposure (chronic acceleration). Plasma glucose, free fatty acids, serum immunoreactive growth hormone, plasma cortisol and urinary epinephrine and norepinephrine were measured prior to and following the infusions of 2-DG. There were significant depressions in glucose, urinary epinephrine, cortisol and free fatty acids following acceleration that were not seen when compared to basal, un-provoked levels. Even with the modest acceleration stresses used in this study discernible changes in gluco-regulatory hormone reserves were uncovered.

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THE HEMODYNAMIC and cardiovascular adaptations to acceleration forces have been well described in man. Considerably less data, however, are available regarding metabolic and endocrine changes. With the design of new high-performance aircraft as well as in exit and re-entry phases of space flight, crewmen are being exposed to higher and more sustained acceleration exposures. Previous studies in which metabolic substrates and hormones were measured have been confined to evaluating basal, fasting pre- and post-acceleration values. Meyer[6] reported elevations in blood sugar during take-off and landings in the NF-100F aircraft which were attributed to epinephrine release secondary to the stress of acceleration. This has been confirmed by Goodall[2] who found elevated urinary catecholamines during and after acceleration. Other investigators have measured parotid 17-hydroxycorticosteroids during take-

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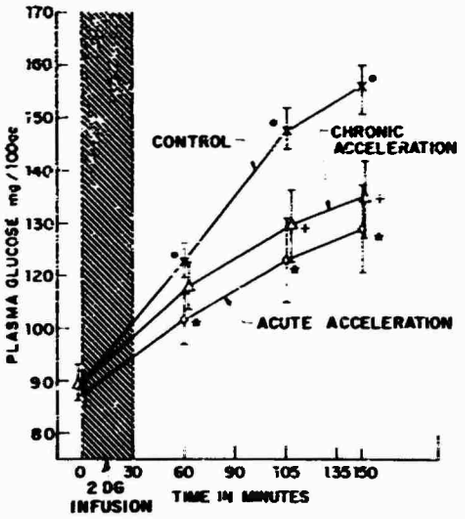

Fig. 1. Plasma glucose response to 2-DG infusion following acute and chronic acceleration (Mean ± S.E.M.) •—+ and •—• refer to significant pairs.

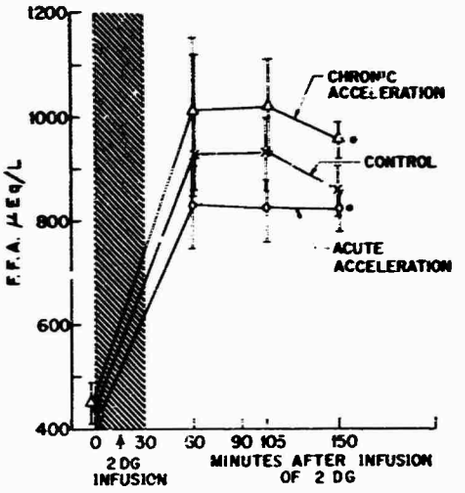

Fig. 2. Plasma free fatty acid (F.F.A.) response to 2-DG infusion after acute and chronic acceleration. (Mean ± S.E.M.) •—• refers to significant pairs.

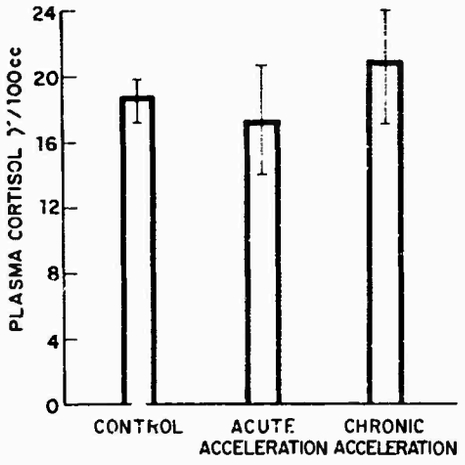

Fig. 3. Mean (± S.E.M.) fasting, post-acceleration plasma Cortisol.

off and landings in aircraft[10] as well as blood ADH concentrations[5] following acceleration. Common to all of these studies, however, has been the reliance on basal hormone concentrations either during or following acceleration without the use of provocative tests that are capable of detecting subtle changes in hormonal reserve.

The present study evaluates pituitary and adrenal hormone reserve in man immediately following gravitational stress. The glucose analogue 2-deoxy-D-glucose (2-DG) was used to stimulate pituitary and adrenal hormone release as described previously.[7-11] The 2-DG administration in humans results in a state of intracellular glucopenia with subsequent reproducible elevations in plasma glucose, free fatty acids, growth hormone, cortisol and catecholamines. The subjects were tested after their initial exposure to the centrifugation (acute acceleration) and after their fourth exposure (chronic acceleration).

METHODS AND MATERIALS

Eight normal, male volunteer basic airmen, ages 18 to 21 years old, were studied. All were within 7% of their ideal weights and had negative family histories for diabetes mellitus and normal oral glucose tolerance tests. The subjects were 14 hours post-absorptive at the time of each study. Their daily diet was constant and contained 300 grams of carbohydrate. Each subject served as his own control throughout the study, four subjects being studied at one time. The study was divided into two parts: First, a five-week control period established each subject's baseline response to weekly infusions of 2-DG; second, the acceleration period in which four separate acceleration exposures occurred over a two-week period with the 2-DG infusions taking place immediately following the first (acute) and fourth (chronic) acceleration exposures.

The 2-deoxy-D-glucose solution was prepared in sterile, distilled water and passed through a 45μ Millipore filter into sterile bottles. Small samples of material were cultured on appropriate culture media and were always free of bacterial contamination. Fifty mg. of 2-DG per/kg of body weight were diluted to 100 ml. with normal saline immediately prior to each infusion. A large catheter was placed in a brachial vein for the purpose of administration of the 2-DG solution and for obtaining blood samples. After obtaining blood samples 15 minutes and immediately prior to the 2-DG infusion, the 2-DG solution was infused at a constant rate for 30 minutes via an infusion pump. Blood was obtained 60 minutes, 105, and 150 minutes after the start of the 2-DG infusion for the determination of plasma glucose, free fatty acids, cortisol and serum immunoreactive growth hormone. Urine was collected from the start of the infusion and for a total of 6 hours for the determination of urinary epinephrine and norepinephrine. The blood samples were stored in ice, centrifuged in a refrigerated centrifuge and kept frozen at −15° C. The urines were preserved in hydrochloric acid and refrigerated until the following day at which time the analyses were performed. Plasma glucose was determined on the Auto-Analyzer using the potassium ferrocyanide-potassium

ferricyanide method.[3] Free acids were determined by the method of Dole.[1] Plasma cortisol was determined by a simplified fluorometric method.[5] Serum immunoreactive growth hormone was done in duplicate by the method of Utiger et al.[4] Urinary epinephrine and norepinephrine were determined by the method of Von-Euler and Lishajko.[2]

The experimental acceleration profile on the human centrifuge for each subject involved a rapid onset acceleration to 2G, holding at 2G for 30 seconds, and then accelerating in 0.5G increments up to a maximum of 4G with a plateau at the 0.5G stages being held for 30 seconds each. Normally, an end point of peripheral light loss occurred during some portion of the 4G stage; however, several subjects were able to continue the full 30 seconds at this stage with no visual impairment. However, the purpose of the exposure was to have a reproducible exposure time and not particularly to expose the man to a blackout episode in which the run, by necessity, would be halted. The subjects were seated upright in a standard fighter aircraft seat with the inertial vector acting in a head-to-foot direction ($+G_z$ acceleration). They were encouraged to relax as much as possible during the exposure and intermittently during the run were offered random peripheral and central lights which they responded to by turning off with finger control switches. This acceleration period was repeated four times during the two-week interval on each subject. All of the acceleration sessions and subsequent infusions of 2-DG were done in forenoon, fasting state. Analyses of variance for randomized groups were done and when significant F values were obtained, paired "t" tests between individual groups were then performed. The level of significance was set at the 0.05 level throughout the study.

RESULTS

Plasma Glucose Responses to Acute and Chronic Acceleration—The mean plasma glucose concentrations prior to and following the 2-DC infusions during the control period and after the initial and 4th acceleration sessions are displayed in Figure 1. There were no significant changes in mean fasting plasma glucose concentrations prior to the 2-DC infusions when control and acceleration data were compared. However, there were significant decreases in the mean plasma glucose response at the 60, 105, and 150 minute sampling periods following 2-DG administration after the acute acceleration and at the 105 and 150 minute period after the chronic acceleration as compared to the control response.

Free Fatty Acid (FFA) Response to Acute and Chronic Acceleration—Mean FFA response to the 2-DG infusion for the control as well as acute and chronic acceleration is shown in Figure 2. Similar to the glucose results there were no significant differences in mean fasting FFA's between the three test periods. Moreover, there were no significant differences between the control and the chronic acceleration mean FFA response to 2-DG administration. However, there was a decreased FFA response following the acute acceleration 2-DG infusion when compared to the chronic acceleration infusion which reached significant levels at the 150-minute time period.

Mean Plasma Cortisol Response to 2-DC Infusion Following Acute and Chronic Acceleration—Mean plasma fasting cortisol concentrations during the control period and following acute and chronic acceleration were not significantly different (Figure 3). The mean plasma cortisol responses to the 2-DG infusion are given in Figure 4. While there were no significant changes in fasting pre-infusion plasma cortisol concentrations when comparing the control group and the plasma obtained immediately after the two acceleration sessions prior to the 2-DG infusion, there were significant differences in mean plasma cortisol response to the 2-DG infusion at the 60, 105, and 150-minute periods when comparing the mean control infusions with acute acceleration 2-DG infusion. Mean plasma cortisol elevations during the

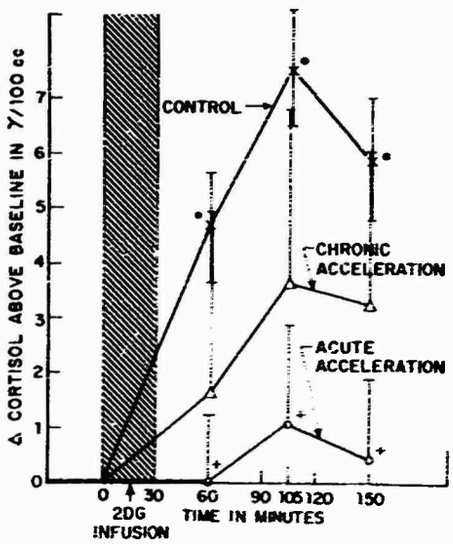

Fig. 4. Mean (± S.E.M.) plasma cortisol increment above the fasting post-acceleration baseline following 2-DG infusion. *—+ indicates sigaificant pairs.

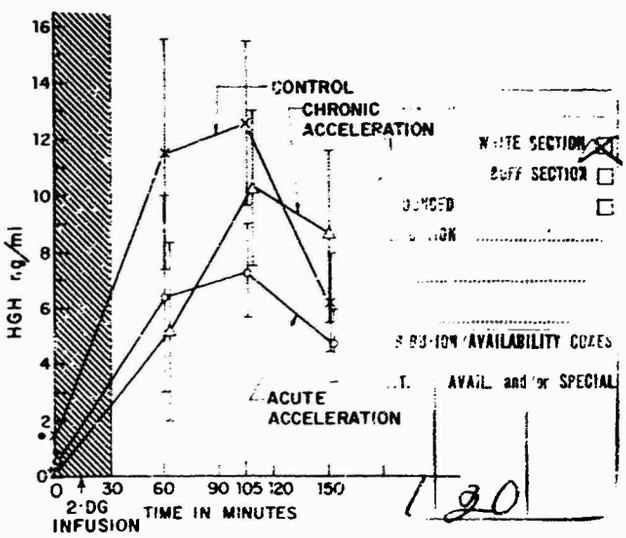

Fig. 5. Immunoreactive growth hormone response to 2-DG infusion following acute and chronic acceleration.

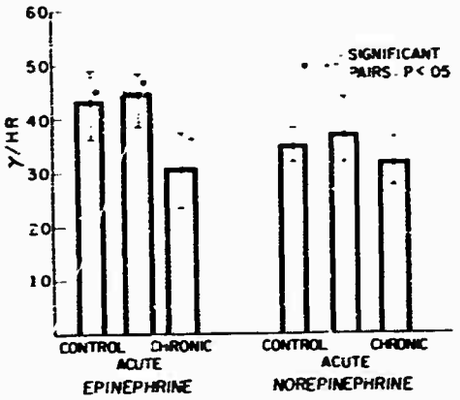

Fig. 6. Urinary epinephrine and norepinephrine response to 2-DG infusion following acute and chronic acceleration. (mean ± S.E.M.)

chronic (or 4th) acceleration session were less marked than the control infusions but did not reach significant levels.

Mean Human Growth Hormone (HGH) Response to 2-DG Infusion—The fasting, pre-infusion mean HGH concentrations as well as the response to the 2-DG infusions are illustrated in Figure 5. Although there was a decreased response in mean fasting HGH immediately after the 4th acceleration sessions when compared with the control values, such low values are difficult to interpret and may not represent a real change. Following the 2-DG infusion there was the expected rise in plasma HGH concentrations during all of the three infusion periods, without significant differences among any of the three groups.

Urinary Epinephrine and Norepinephrine Response Following 2-DG Infusion—Mean urinary epinephrine and norepinephrine excretion values expressed as gamma/hr are shown in Figure 6. There was a significantly decreased response in the epinephrine excretion during the 2-DG infusion that followed the chronic acceleration session as compared to the excretion obtained during the control periods and during the infusion performed following the acute acceleration. There were no significant differences in norepinephrine excretions following 2-DG infusion during any of the three periods.

DISCUSSION

Even though only modest acceleration forces were used in this study, there were alterations in substrate and hormone response to 2-DG administration. It is important to note that the alterations would not have been detected if only basal, unprovoked values pre- and post-acceleration exposure were compared to the control. The implication that can be made from this observation is that acceleration stress to the degree imposed upon the subjects in this study resulted in a decrease in pituitary and adrenal reserve but did not deplete the hormonal stores completely. While there were no changes in fasting-basal glucose, cortisol and free fatty acid concentrations immediately after acute and chronic acceleration, there were significant depressions in the response of these substances to 2-deoxy-D-glucose stimulation following the acceleration exposure. The apparent normal growth hormone response to 2-DG following acceleration suggests either intact pituitary reserve or changes which were too subtle to be detected by the techniques employed.

Measurements of other pituitary hormones, such as TSH, ACTH and the gonadotrophins are needed in order that pituitary function after acceleration may be fully evaluated. The blunted response in plasma cortisol concentrations and epinephrine excretion following 2-DG stimulation after acceleration suggests a significant decrease of adrenal reserve. Since the substances measured in this report reflect not only production or release rates but also utilization rates by target tissues, the possibility that utilization is increased following acceleration was considered. The appropriate measurements to evaluate disappearance rates were not accomplished, however, leaving this latter possibility strictly a matter of speculation. Both acute acceleration and chronic acceleration appear to be a far more stressful situation as far as endocrine function is concerned than has been previously recognized. The alteration in endocrine adaptation to acceleration may play an important role in future prolonged manned space flight where multiple prolonged acceleration exposures are involved.

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13. ABSTRACT

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